



**Trip Report:  
229<sup>th</sup> ACS Meeting  
San Diego Convention Center,  
San Diego, California  
March 13 – 17, 2005**

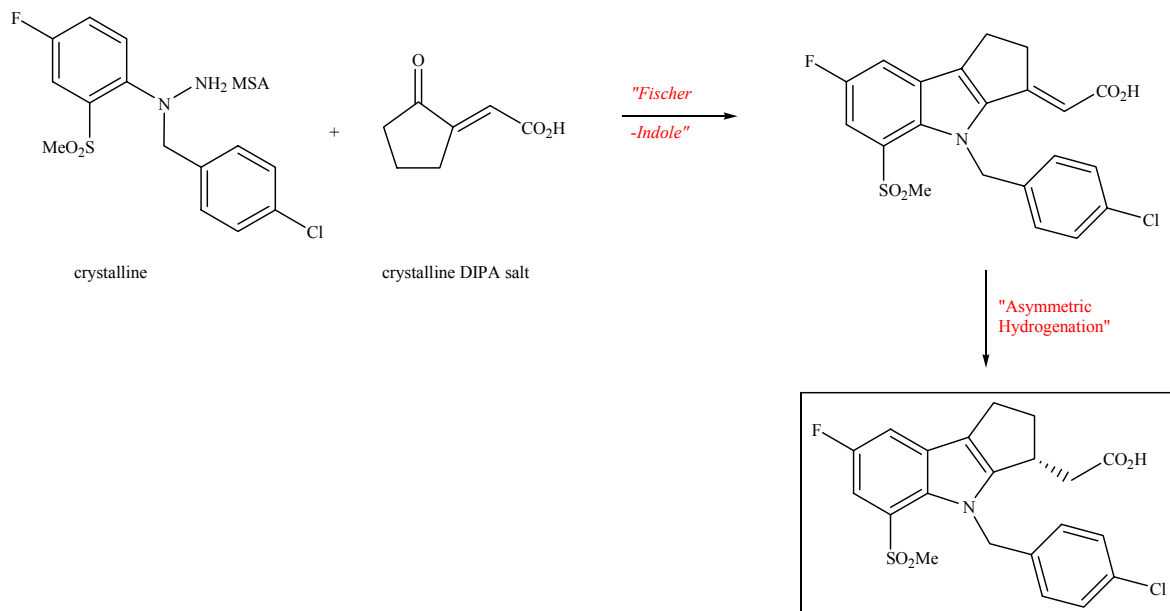
**Jonathan Hutchinson and Andrew J. Locke, Ph.D.**

cGMP Department  
Albany Molecular Research, Inc.  
21 Corporate Circle  
Albany, NY 12212

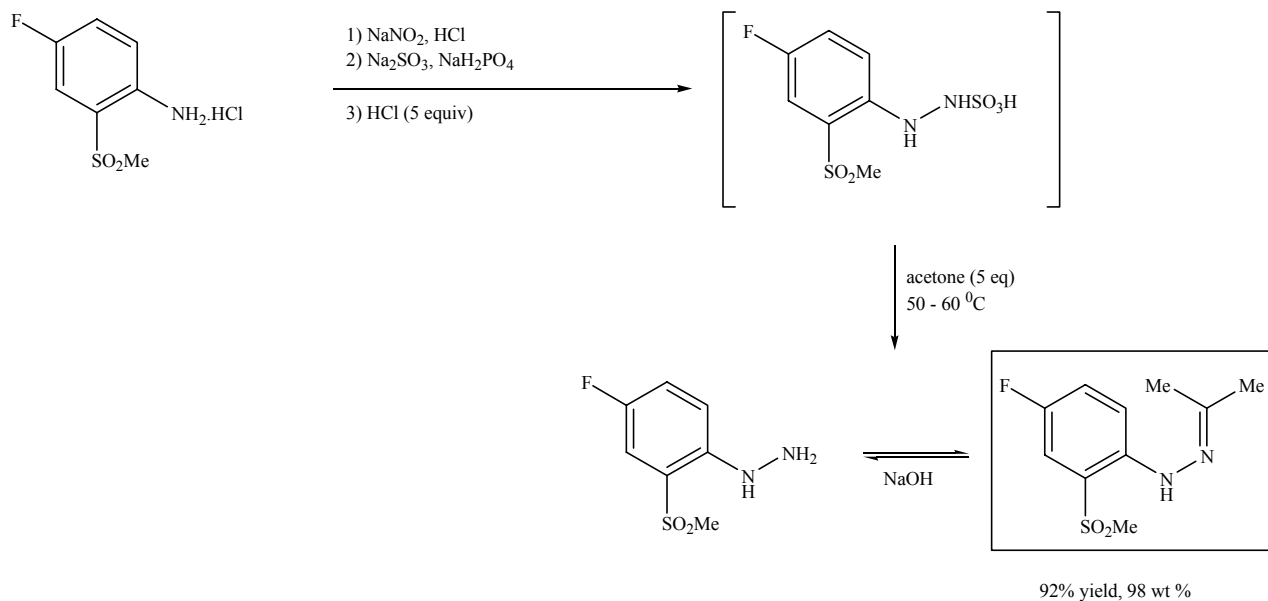
***Abstract:** The 229<sup>th</sup> ACS National Meeting was held in San Diego, California on March 13-17, 2005. Numerous lectures and posters were presented, of which, selected topics of interest are summarized. Here is the trip report of Andrew J. Locke, Ph.D. and Jonathan Hutchinson from the cGMP Department.*

## Development of a Practical Asymmetric Synthesis of a DP Receptor Antagonist, Zihui Peng, Process Research, Merck & Co., Inc., NJ 07065.

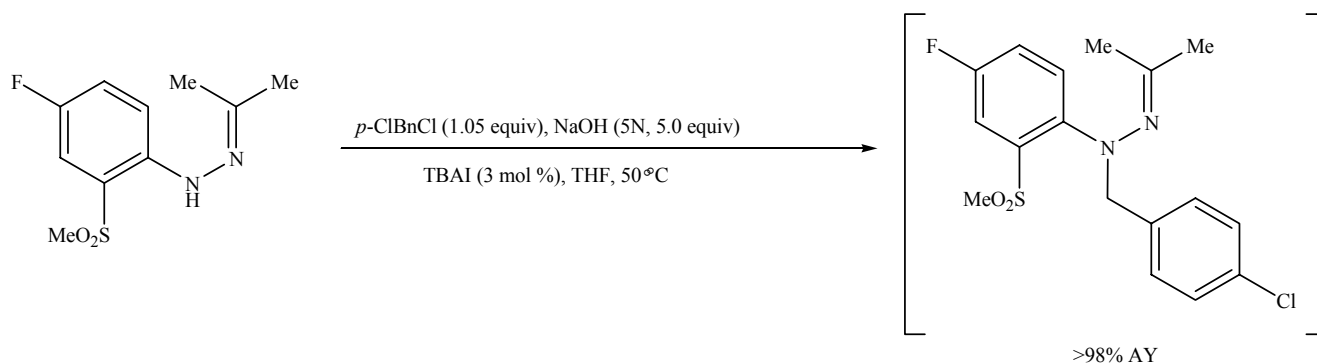
A highly convergent and practical asymmetric synthesis of a DP receptor antagonist has been developed. The reaction involves a Fischer-indole synthesis and an asymmetric hydrogenation reaction.



### Hydrazine Synthesis (I): Isolation of Acetone Hydrazone

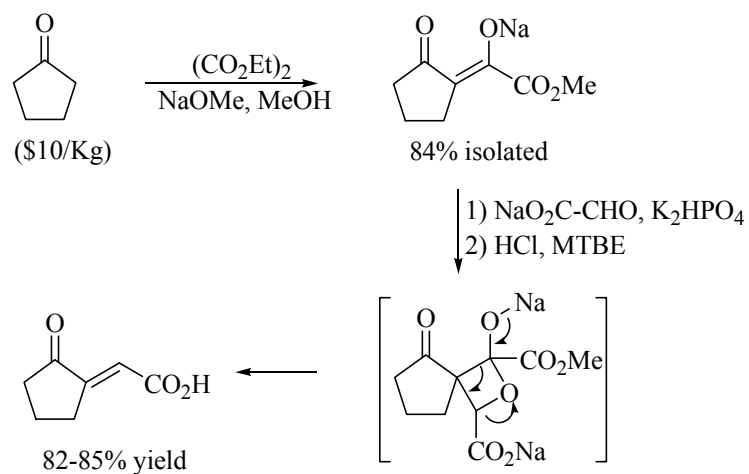


## Benylation of the Acetone Hydrazone and Crystallization-Driven Hydrolysis



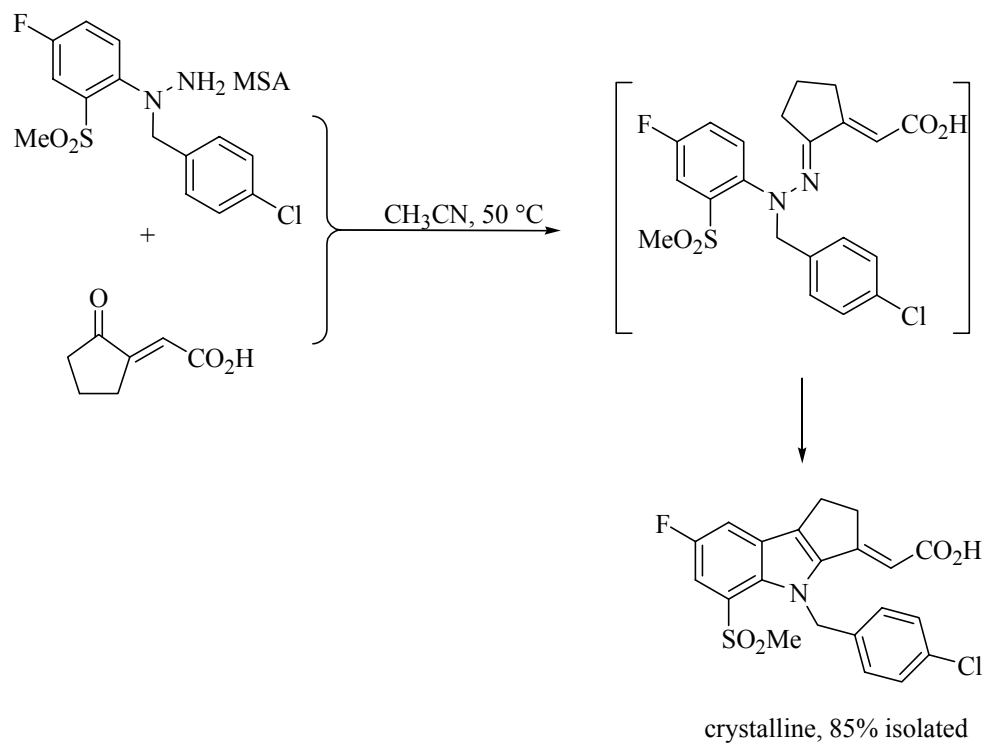
- The benzylhydrazine can be isolated as free base or MSA salt or directly used in the next step.

## Oxo-ene Acid Synthesis



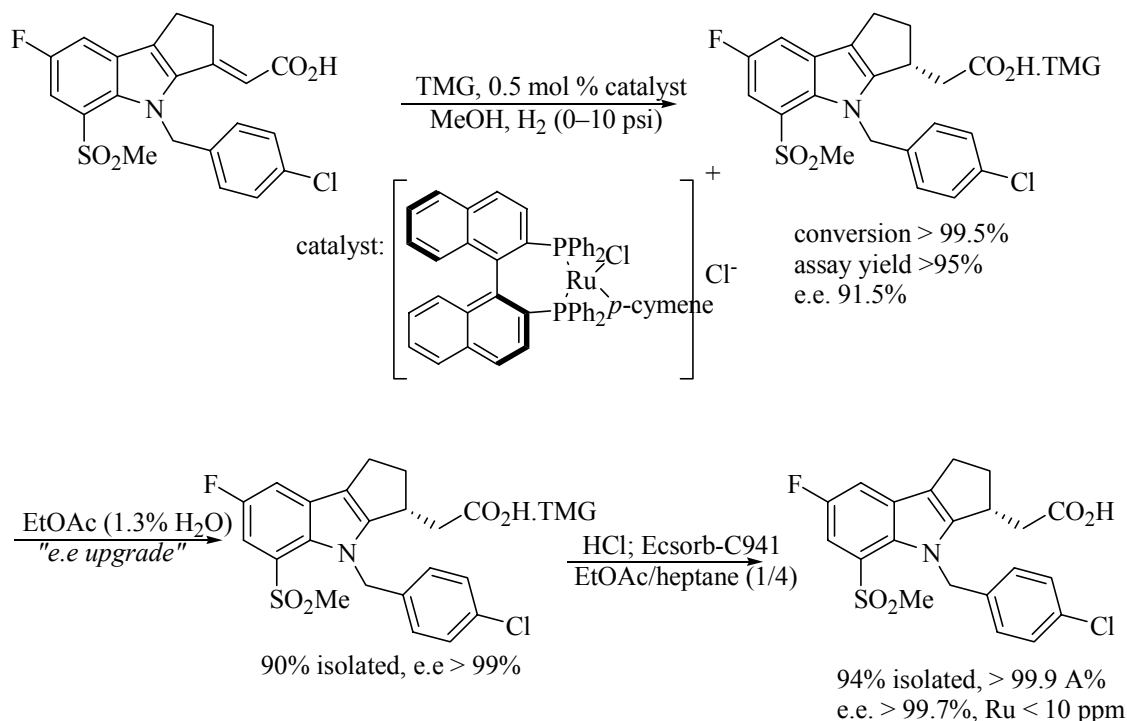
- Readily available, inexpensive starting materials.
- Isolated as either free-acid or as crystalline diisopropylamine salt.

## Fischer-Indole Synthesis



- Ene-acid directly crystallized from reaction.

## Asymmetric Hydrogenation and Final Processing



TMG salt easily isolated, exhibits good solubility properties, and serves as a suitable cation for the upgrade of chiral purity.

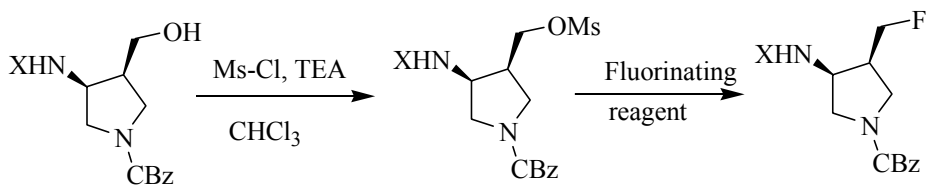
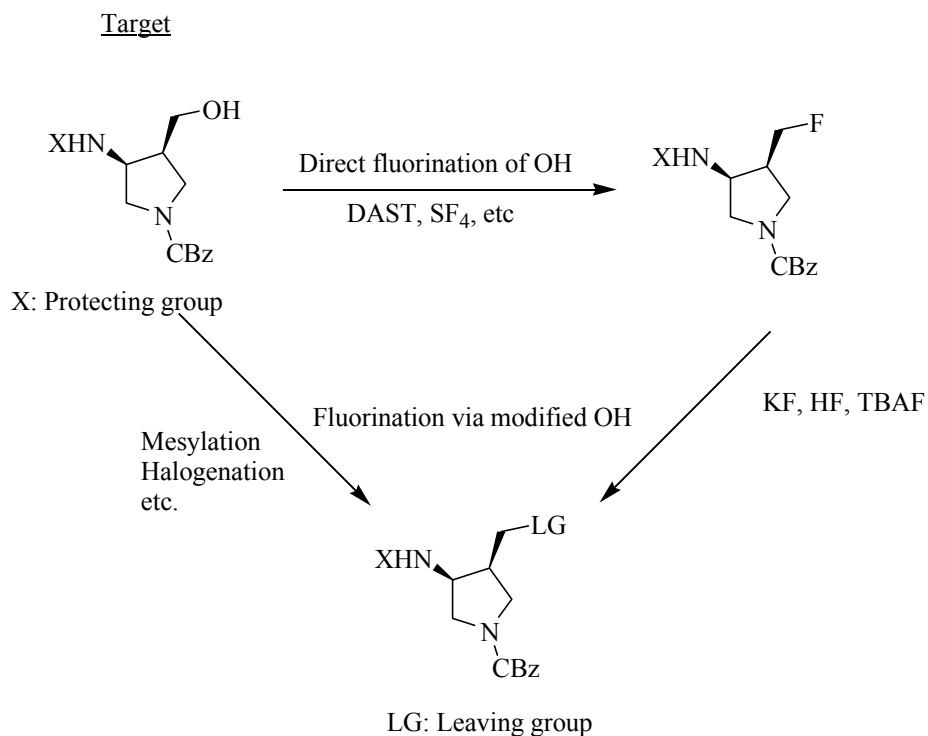
### Summary

- Convergent synthesis, cheap starting materials, high yielding (5 chemical steps, 52% overall yield).
- Asymmetric synthesis: asymmetric hydrogenation at the last step.
- Crystalline intermediates, outsourcing opportunities
- Manufacturing route identified.

### Discovery, Implementation, and Mechanism of a Pressure-dependent Catalytic, Asymmetric $\alpha, \beta$ -Unsaturated Carboxylic Acid Hydrogenation.

David M. Tellers, J. Chris McWilliams, Department of Process Research Inc., PO Box 2000, Rahway, NJ

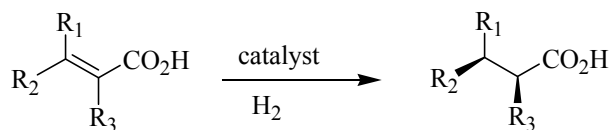
The asymmetric hydrogenation of  $\alpha, \beta$ -unsaturated carboxylic acids is a useful method for preparing chiral carboxylic acid derivatives.



The reaction proceeded in the moderate condition. Carbamate on 3-amino group was suitable for fluorination by TBAF.

## Outline

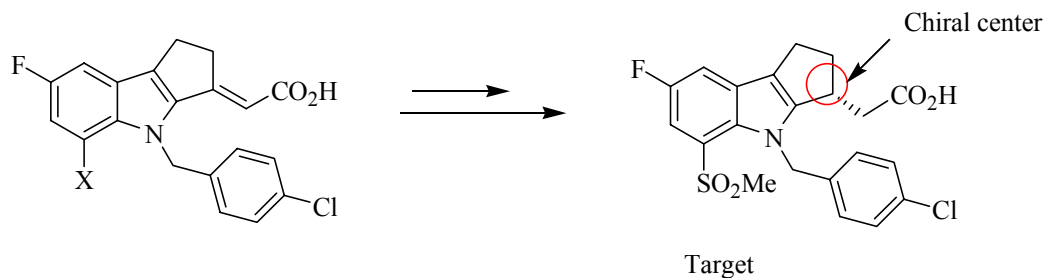
- Ene Acid Hydrogenation background.
- Reaction discovery.
- Optimization.
- Mechanistic studies.



- Typically ruthenium based with BINAP-type ligand.
- May exhibit pressure dependence.

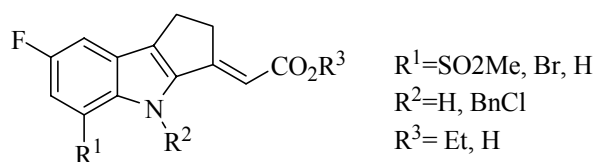
- Acids are typically much more reactive than ester counterpart.

### Ene Acid Asymmetric Hydrogenation



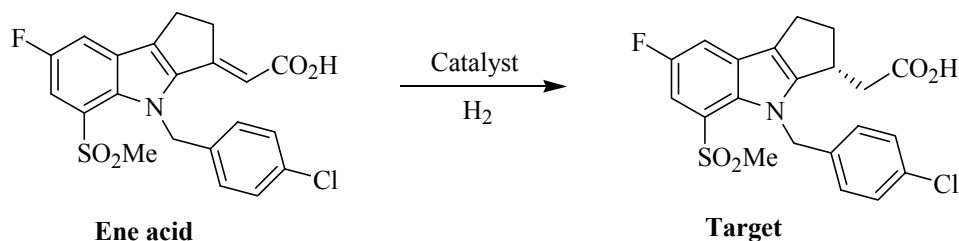
Accessible via enantioselective hydrogenation with a homogenous catalyst.

### Multiple Hydrogenation Candidates are Evaluated



Asymmetric hydrogenation development occurs “real time.”  
 Screened library of Rh and Ru catalysts, identified 10 hits.

### Hydrogenation of the Penultimate



### Advantages

- Sets chiral center last.
- Avoids loss of expensive chiral intermediates.
- Supports/facilitates convergent synthesis.

### Disadvantages

- Upgrade.
- Metal removal.
- Substrate purity and catalyst loading.

## Hydrogenation Base/solvent Selection

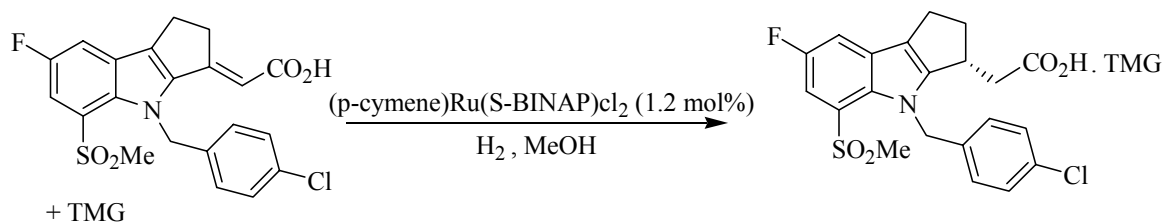
- Ene acid exhibits poor solubility in “practical” hydrogenation solvents.

Solvent	mg/mL	Solvent	mg/mL
MeOH	0.019	Toluene	0.008
EtOH	0.016	Acetonitrile	0.02
DMAC	20.2	EtOAc	0.06
DMF	9.7	DMSO	19.4
THF	0.09	Acetone	0.11

- Salt formation greatly increases ene acid solubility in MeOH.

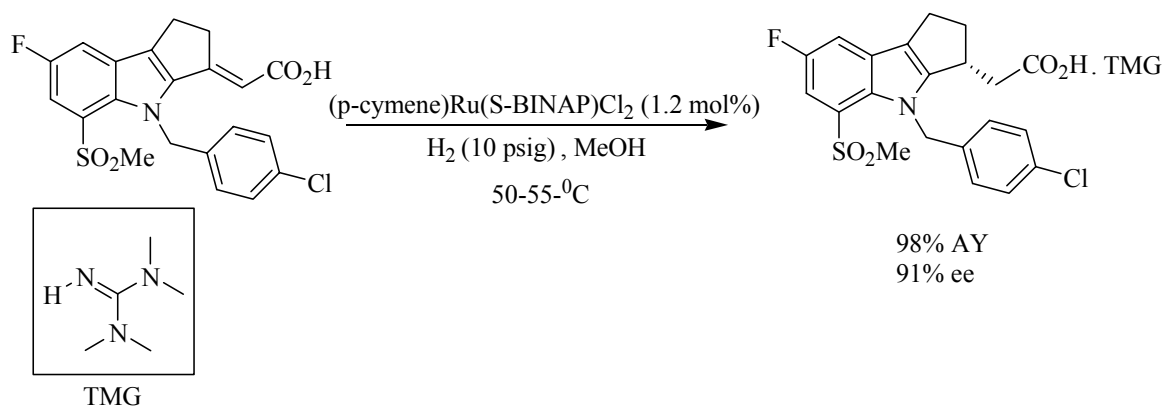
Base	mg/mL
Et <sub>3</sub> N	7.8
Cs <sub>2</sub> CO <sub>3</sub>	>300
KOtBu	>200
Tetramethylguanidine	183

## Affect of Temperature and Pressure on Enantioselectivity



- Results show increasing pressure has negative impact on enantioselectivity.

## Optimized Process: Hydrogenation of Penultimate



- Chiral center installed as last step (hydrogenation of sulfone ene acid).
- Catalyst prepared in situ tetramethylguanidine (TMG) used as base for rate and upgrade of chiral purity.

- Low hydrogen pressure crucial for good enantioselectivity

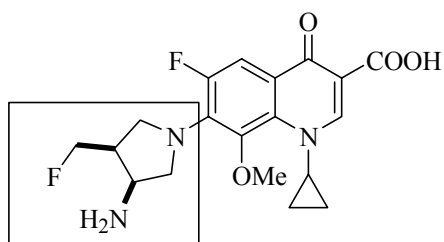
### Summary and Conclusions

- A pressure-sensitive ene acid hydrogenation was successfully demonstrated.
- E and Endo isomers of the ene acid are in a metal catalyzed equilibrium.

### Process Research and Scale up for the Practical Fluorination for the Preparation of (3R)-Amino-(4R)-fluoromethyl Pyrrolidine.

Satoshi Takei, Daiichi Pharmaceutical Co. Ltd. Chemical Research Center, 1-16-13, Kitakasai, Edogawa, Tokyo 134-8630 Japan

DC-756 was found to be a new potent quinolone antibacterial agent. The synthesis of DC-756 required the development of the preparation of the key building block pyrrolidine



DC-756

### Introduction

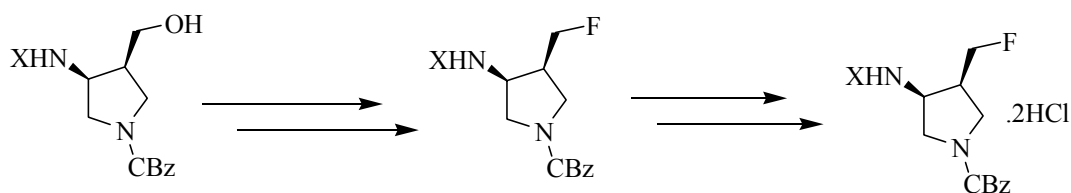
#### (3R)-Amino-(4R)-fluoromethyl-pyrrolidine

- Very useful intermediate for the substituent at C-7 position of quinolone analog DC-756.

#### Points to Synthesize the Key Intermediate

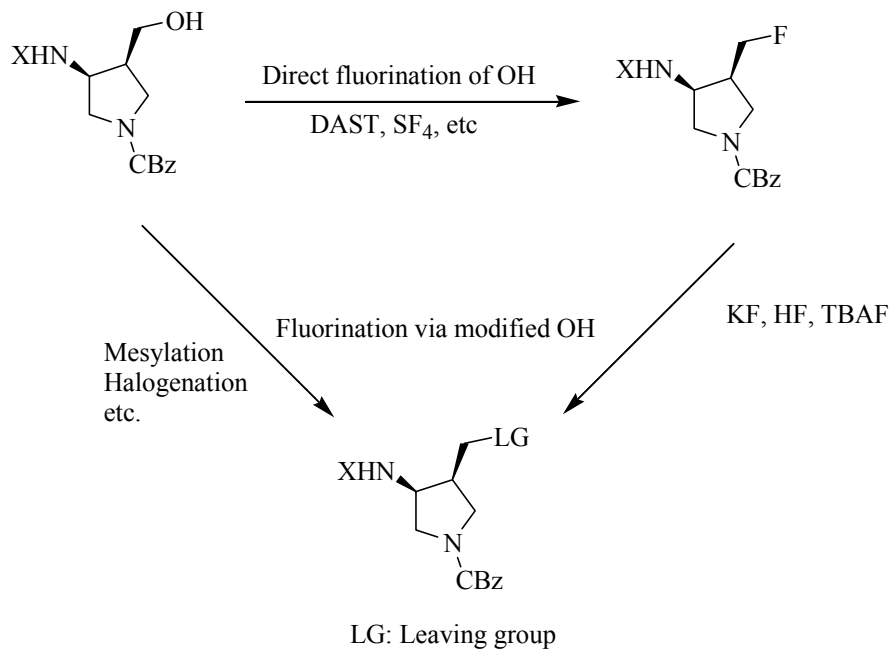
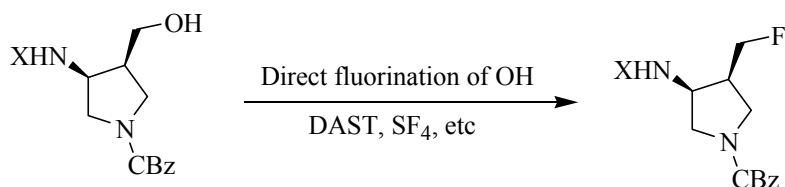
- Control of two enantiomeric centers.
- Fluorination of hydroxyl group.

#### Target

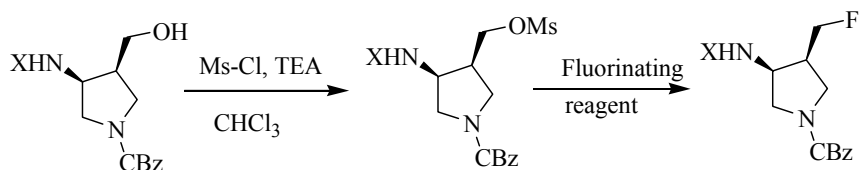


- Investigation of the most suitable substrate and reaction condition.
- Development for the largest scale preparation.

#### Strategy for Fluorination of Hydroxyl Group

Target**Direct Fluorination of Amino Hydroxyl Pyrrolidines**

Very low yield due to harsh conditions.

**Fluorination of Amino Hydroxyl Pyrrolidines via Mesylate**

The reaction proceeded in the moderate condition. Carbamate on 3-amino group was suitable for fluorination by TBAF.

## Conclusion

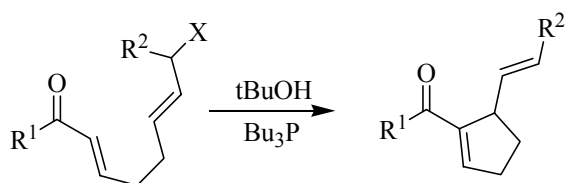
Succeeded to find the most suitable fluorination method.

The most suitable substrate: Boc on NH<sub>2</sub>, OH -> OMs.

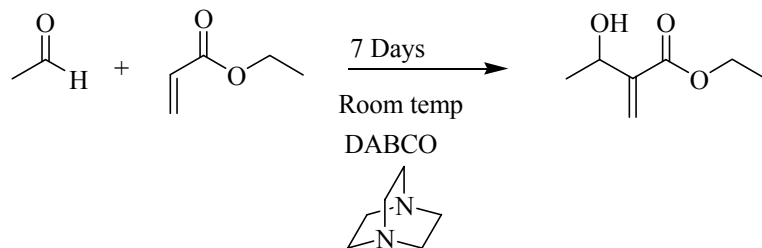
## Intramolecular Morita-Baylis-Hillman Cycloallylation Reactions.

Marie E. Krafft and Thomas F. N. Haxell, Department of Chemistry, Florida State University, Tallahassee, FL

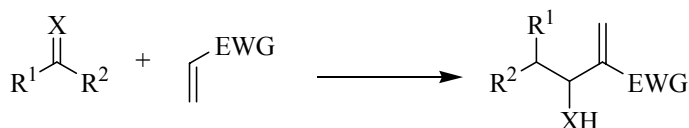
The Morita-Baylis-Hillman reaction is a three component reaction in which Michael acceptors are coupled at the alpha-position to electrophilic carbonyl compounds under the influence of a nucleophilic catalyst. This method has been extended to include intramolecular examples bearing allylic leaving groups which provide a facile, high yielding straightforward synthesis of densely functionalized cyclic molecules.



## Baylis-Hillman Reaction



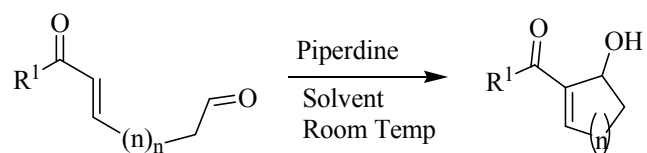
## Scope/limitations



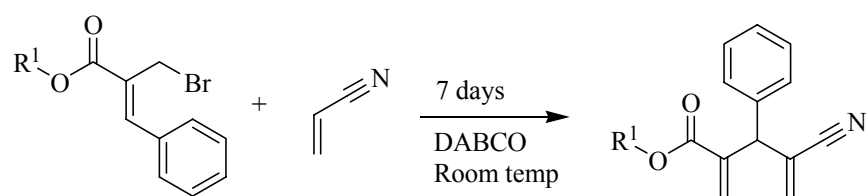
## Activated Alkenes

- Electrophiles.
- Nucleophilic catalyst- 3<sup>o</sup> amines or phosphine.
- Reaction 3<sup>rd</sup> order – days to weeks.
- Activated alkene β- β unsubstituted.
- Not been extended to unactivated allylic leaving groups.

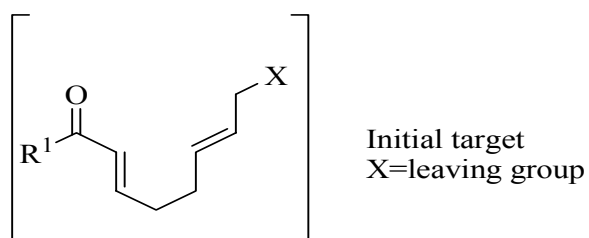
## Investigation of Electrophiles



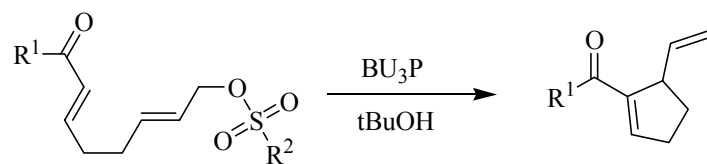
## Allylic Electrophiles



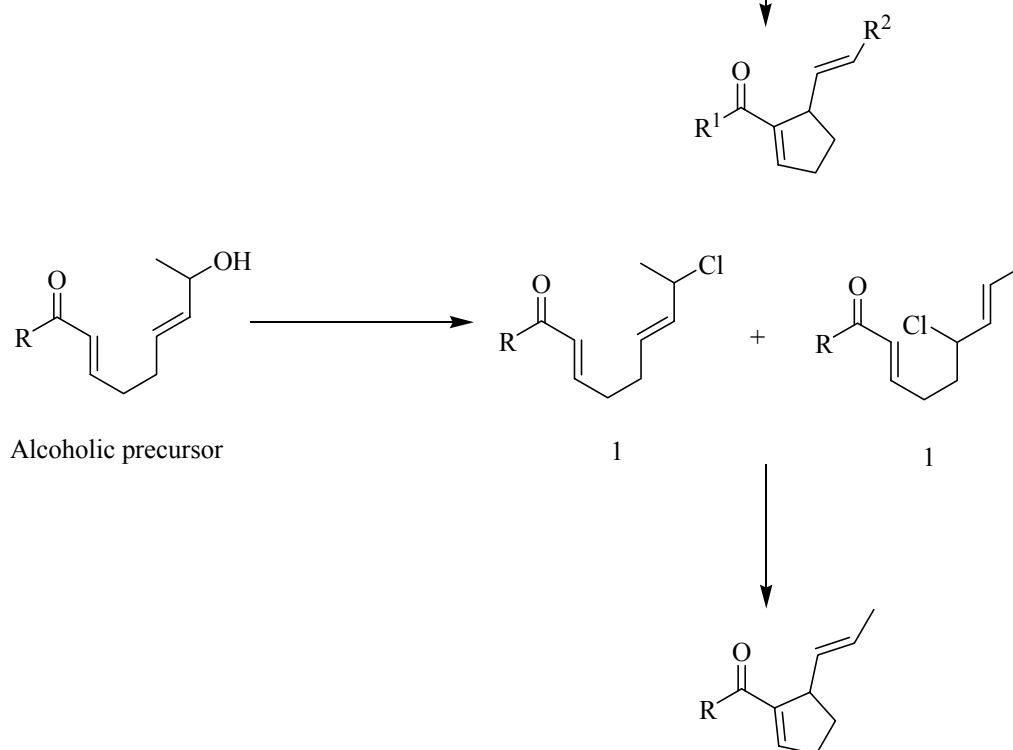
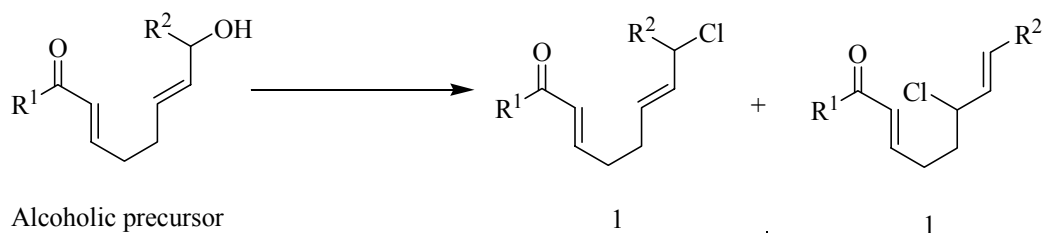
## Substrate Preparation



Choice of leaving group. Can choose OMs or OTs.



R= Me or Tol

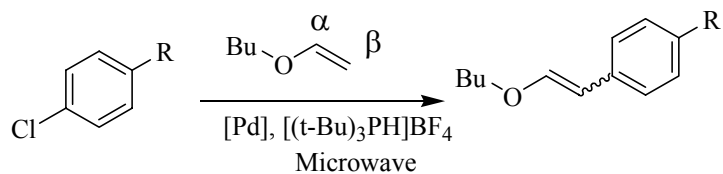
**New Substrate**

This method has been extended to include intramolecular examples bearing allylic leaving groups which provide a facile, high yielding straightforward synthesis of densely functionalized cyclic molecules.

**Regioselective Terminal Heck Arylations of Vinyl Ethers with Aryl Chlorides.**

Gopal K. Datta, Henrik von Schenck, Mats Larhed and Anders Hallberg, Department of Medicinal Chemistry, Organic Pharmaceutical Chemistry, BMC, Uppsala University, Box 574, SE-751 23 Uppsala, Sweden

Among available C-C coupling reactions, the palladium-catalyzed Heck Reaction is one of the most important methods. The fundamental problem of performing regioselective terminal heck arylations of alkyl vinyl ethers using aryl chlorides has remained unsolved. Here is a novel and general  $\beta$ -selective microwave protocol of the achieved high regioselectivity.



[Pd] = Hermann's palladacycle = [trans-Di( $\mu$ -acetato) bis [o-(di-o-tolylphosphino)benzyl]dipalladium(II)].

### Reaction Conditions

- Hermann's palladacycle (5.0 mol %), [(t-Bu)<sub>3</sub>PH]BF<sub>4</sub> (10 mol %), aryl chloride (1.0 mmol), butyl vinyl ether (2.0–3.0 mmol), Cy<sub>2</sub>NMe (3 mmol)/ PMP (5 mmol), DMF:H<sub>2</sub>O (2 mL : 200  $\mu$ l)/PEG 200 2 mL, 160 °C, 60 min.

### Conclusion

- A rapid palladium-catalyzed regioselective terminal arylation of vinyl ethers with both electron poor and electron rich aryl chlorides.
- A large improvement in  $\beta$ -selectivity from the release of bulky (t-Bu)<sub>3</sub>P.